

REMARKS

Reconsideration of the present application is respectfully requested in view of the following Remarks. Claims 33-86 are pending in the application: claims 73-80 are currently under examination and claims 33-72 and 81-86 are withdrawn. Applicant thanks the Examiner for acknowledging the allowable subject matter in claims 79-80.

Rejections Under 35 U.S.C. § 103

The Examiner rejects claims 73-78 under 35 U.S.C. § 103(a) for alleged obviousness over Kelly (WO 93/23069) in view of Guggolz *et al.* (*Agr. Food Chem.*, 9:330-332 (1961)). The Examiner asserts that Kelly teaches a composition comprising two or more components from leguminous plants, including formononetin and biochanin A, and that Guggolz *et al.* teach the distribution of isoflavones in various crops. The Examiner then asserts that it would have been obvious to one of ordinary skill in the art to modulate the ratio of formononetin and biochanin A in Kelly to achieve an optimum ratio in view of Guggolz *et al.*

Applicant traverses this assertion and submits that the instant claims satisfy the requirements of non-obviousness. In particular, Applicant submits that the Examiner has not established a *prima facie* case of obviousness with respect to the presently claimed subject matter. (See *In re Mayne*, 104 F.3d 1339 (Fed. Cir. 1997); the USPTO has the burden of showing a *prima facie* case of obviousness). The Examiner must at a minimum demonstrate that the combined references teach or suggest all the claim features, and even assuming, *arguendo*, that the combination of references teaches each claim feature, the Examiner must provide an explicit, apparent reason to combine these features in the fashion claimed by the Applicant with a reasonable expectation of success. See *KSR v. Teleflex, Inc.*, No 04-1350 at 4, 14 (U.S. Apr. 30, 2007) (“A patent composed of several elements is not proved obvious merely by demonstrating that each element was, independently, known in the prior art”). In the instant case, the cited references, alone or in combination, fail to teach or suggest a composition comprising an effective amount of formononetin and biochanin A, wherein the level of biochanin A is less than about 10% w/w of the isoflavone content, and wherein genistein, if present, is in the amount of less than about 5% w/w.

Kelly fails to teach each feature of the instant claims, and in particular fails to teach or suggest a composition comprising an effective amount of formononetin and biochanin A, wherein the level of biochanin A is less than about 10% w/w of the isoflavone content, and wherein genistein, if present, is in the amount of less than about 5% w/w. Kelly merely teaches the importance of a composition comprising genistein and daidzein in approximately equal proportions (*see, e.g.*, Kelly, page 10, paragraph 3), wherein the ratio between these two components, or their methylated forms (*i.e.*, biochanin A and formononetin), varies between about 1:2 or 2:1. Kelly emphasizes in particular the importance of genistein, which has greater activity than all the other isoflavones (*see, e.g.*, Kelly, page 9, paragraph 5), and emphasizes as well that formononetin in particular has the least activity of all the isoflavones (*see, e.g.*, Kelly, page 9, paragraph 4). The isoflavone ratio as recited in the instant claims is thus far outside the range described in Kelly, and is directed as well to a composition that favors formononetin, the least active isoflavone according to Kelly.

Guggolz *et al.* fail to remedy the defects in Kelly. Guggolz *et al.* is merely a research paper from 1961 that describes the detection (using paper chromatography) of various forage estrogens in several different plants. Guggolz *et al.* clearly do not teach or suggest a composition as presently claimed, let alone does this reference teach or suggest an optimum, effective isoflavone ratio in favor of formononetin and biochanin A, as recited in the instant claims. Applicant submits that neither Kelly nor Guggolz *et al.*, alone or in combination, teach a composition comprising the particular ratio of isoflavones as presently claimed, and thus further submits that the cited references fail to render obvious the presently claimed subject matter.

Even assuming, *arguendo*, that the cited references in combination teach each feature of the instant claims, these references provide no apparent reason to combine their teachings with a reasonable expectation of success. In fact, Kelly provides no apparent reason at all to modulate the isoflavone ratio in favor of formononetin and biochanin A, let alone does Kelly provide an apparent reason to produce a composition comprising less than about 5% w/w of genistein, as recited in the instant claims. In contrast to the instant application, Kelly emphasizes the importance of genistein's therapeutic biological activities, and de-emphasizes the importance of formononetin (*see, e.g.*, Kelly, page 9, paragraphs 5-6). Kelly relies mainly on

genistein and daidzein, and teaches that it is prudent that these isoflavones be present in approximately equal proportions (*see, e.g.*, Kelly, page 10, paragraph 3); suggesting that the presently claimed compounds would have little, if any therapeutic biological activity. Kelly thus fails to provide a person of ordinary skill in the art with an apparent reason to formulate a formononetin-based composition as presently claimed, and fails as well to provide a reasonable expectation that such a composition would possess the therapeutic qualities described in the instant application.

Guggolz *et al.* do not compensate for the defects in Kelly, as Guggolz *et al.* nowhere even remotely mention or suggest the biological efficacy of any specific isoflavone in relation to the others, such as in the treatment or reduction of menopausal symptoms in a post-menopausal woman. In fact, Guggolz *et al.* merely describe the relative abundance of based on ppm in dry forage of daidzein, formononetin, genistein, biochanin A, and coumestrol. The sole comment in Guggolz *et al.* related to bioactivity is directed to coumestrol, wherein the authors state that coumestrol is more than 30 times as estrogenic as any of the isoflavones. Clearly such a teaching does not motivate one to combine this art with Kelly as it does not add any relevant information, quite the contrary is true, as this article would teach one to use coumestrol as opposed to any of the isoflavones. Accordingly, absent any such teachings to contradict Kelly, a person skilled in the art would find no apparent reason to modulate the isoflavone ratios as taught in Kelly in favor of formononetin and biochanin A, and would thus find no reasonable expectation of success in using such a composition to prevent or reduce menopausal symptoms.

In addition, Applicant respectfully disagrees with the Examiner's assertion that it would have been obvious (*i.e.*, involving only routine experimentation) to modulate the ratio of Kelly in view of Guggolz *et al.* in arriving at the presently claimed subject matter. For one, Guggolz *et al.* simply do not teach or suggest an optimum ratio that in any way relates to the composition as presently claimed. Moreover, the selection of a compound comprising an effective amount of formononetin and biochanin A, wherein the biochanin A is less than about 10%, and genistein, if present, is less than about 5% w/w, represents a selection made from a large number of possible combinations based on the disclosure of Kelly. Among such a large number of possibilities, a person of ordinary skill in the art would not arrive at the presently

claimed composition without some direction or suggestion in the art, which, as noted herein, is entirely absent from the cited references.

Applicant also notes that before the Examiner characterizes the determination of optimum ranges of a given variable as routine or obvious, that particular variable must first be recognized as a result-effective variable (*i.e.*, a variable that achieves a recognized result). See M.P.E.P. §2144.05 (II)(B), citing *In re Antonie*, 559 F.2d 618, 195 USPQ 6 (CCPA 1977). In the instant case, the cited references, alone or in combination, do not teach or in any way recognize that formononetin represents a result-effective variable for treatment or reduction of menopausal symptoms in a post-menopausal woman. In fact, as noted herein, Kelly teaches that formononetin has the least biological activity of all the isoflavones, whether *in vitro* or *in vivo* (*see, e.g.*, Kelly, page 9, paragraph 4), and Guggolz *et al.* does not remedy this teaching. The cited references thus fail support the Examiner's assertion that modulating the ratio of isoflavones around a previously unrecognized result-effective component, such as formononetin, involved routine or obvious experimentation.

In contrast to the cited art, the instant specification teaches that formononetin may represent a result-effect variable, by describing, for example, that administering formononetin to post-menopausal women relative to a control group both decreases menopausal symptoms, as measured by the Greene Score, and improves signs of osteoporosis, as measured by bone density and bone turnover markers (*see, e.g.*, page 18, lines 1-10 of the specification). Applicant therefore submits that the only way the Examiner can assert that it would have been obvious (*i.e.*, involving only routine experimentation) to optimize the isoflavone ratios around the biological effects of formononetin, as in the instant claims, is to rely on impermissible hindsight using the disclosure in the instant specification.

Moreover, even assuming, *arguendo*, that it would have been *prima facie* obvious to modulate the ratio of Kelly to achieve an optimum ratio as presently recited in the claims, Applicant can rebut by showing that "there are new and unexpected results relative to the prior art." *Iron Grip Barbell Co., Inc. v. USA Sports, Inc.*, 392 F.3d 1317, 1322 (Fed. Cir. 2004). Here, the instant application discloses new and unexpected results relating to the use of formononetin in reducing post-menopausal symptoms. In particular, and contrary to the

understanding in the prior art, the instant application teaches that desirable clinical results may be achieved regardless of whether genistein and daidzein are both present in an isoflavone-related composition, let alone whether these particular isoflavones are present in approximately equal proportions (*see, e.g.*, Example 6 on page 18 of the specification). In addition, the *in vivo* pharmacokinetic studies described in the instant application teach the surprising result that formononetin (*i.e.*, the methyl form of daidzein) is not largely demethylated to daidzein, and in fact persists in the body in its unmetabolized form for a considerable time (*see, e.g.*, page 17, lines 21-30). This observation runs contrary not only to the cited prior art, but runs contrary as well to previous opinion in the isoflavone-related arts (*see, e.g.*, page 17, lines 28-30 of the specification). The relevance of this new and unexpected observation relating to formononetin's persistence in the body is particularly acute when viewed in light of the therapeutic qualities described for this particular isoflavone (*see, e.g.*, Examples 6 & 7, on page 18, lines 1-25), which qualities are unexpected in view of the prior art understanding that demethylation of formononetin improves biological efficacy, and that formononetin has the least activity of all the isoflavones. Accordingly, the new and unexpected results described in the instant application, which optimize the ratio of isoflavones in a manner consistent with the novel observations relating to the role of formononetin in particular, support the non-obviousness of the presently claimed subject matter.

Based on the remarks provided herein, Applicant submits that the Examiner has not established a *prima facie* case of obviousness over the presently claimed subject matter, since none of the cited references, alone or in combination, teach each feature of the instant claims. The cited references further fail to provide an apparent reason to combine their teachings with a reasonable expectation of success in arriving at the presently claimed composition.

Even assuming, *arguendo*, that the Examiner has established a *prima facie* case of obviousness, Applicant has more than adequately rebutted the Examiner's showing by demonstrating new and unexpected results relative to the prior art. Accordingly, Applicant submits that claims 73-78 satisfy the requirements of non-obviousness under 35 U.S.C. § 103(a), and respectfully request reconsideration and withdrawal of the Examiner's rejection to these claims.

Obviousness-Type Double Patenting Rejection

The Examiner provisionally rejects claims 73-78 on the grounds of nonstatutory obviousness-type double patenting for being allegedly unpatentable over claim 1 of co-pending U.S. Application No. 10/611,087, which is the U.S. filing of WO 93/23069 (Kelly). The Examiner asserts that it would have been obvious to modulate the ratio of formononetin to biochanin A in claim 1 of Kelly to achieve an optimum ratio in view of Guggolz *et al.*

Applicant traverses this rejection and submits that the instant claims are non-obvious over claim 1 in U.S. Application No. 10/611,087. In particular, as noted in greater detail herein, Applicant submits that it would not have been obvious to modulate the ratios of formononetin and biochanin A as described in Kelly to achieve an optimum ratio in view of Guggolz *et al.* Applicant notes that the Remarks provided herein under the Examiner's 35 U.S.C. § 103(a) rejection of claims 73-78 apply similarly to the instant rejection.

Accordingly, Applicant respectfully requests reconsideration and withdrawal of this rejection to the claims.

Objections to the Claims

The Examiner objects to claims 79-80 as being dependent upon a rejected base claim. Applicant thanks the Examiner for acknowledging the allowable subject matter in claims 79-80, but, as noted herein, respectfully submits that claim 73, from which the instant claims depend, satisfies the requirements of non-obviousness 35 U.S.C. § 103(a).

Applicant submits that all of the claims in the application are allowable. Favorable consideration and a Notice of Allowance are earnestly solicited.

The Director is authorized to charge any additional fees due by way of this Amendment, or credit any overpayment, to our Deposit Account No. 19-1090.

Respectfully submitted,
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